LP-2016

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07C 227/32, 67/31 — A1

(11) International Publication Number: WO 00/29370

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/IT99/00365

(22) International Filing Date: 12 November 1999 (12.11.99)

(30) Priority Data:
MI98A002477 16 November 1998 (16.11.98) IT

(71) Applicant *(for all designated States except US)*: SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A. [IT/IT]; Viale Shakespeare, 47, I-00144 Rome (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TINTI, Maria, Ornella [IT/IT]; Via Ernesto Basile, 81, I-00182 Rome (IT). PICCOLO, Oreste [IT/IT]; Via Bormò, 5, I-23896 Sirtori (IT). BONIFACIO, Fausto [IT/IT]; Via Guido d'Arezzo, 9, I-04100 Latina (IT). CRESCENZI, Cristina [IT/IT]; Via Appia Nuova, 359, I-00181 Roma (IT). PENCO, Sergio [IT/IT]; Via Milly Carla Mignone, 5, I-20153 Milano (IT).

(74) Agent: SPADARO, Marco; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Viale Shakespeare, 47, I-00144 Rome (IT).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INDUSTRIAL PROCESS FOR THE PRODUCTION OF L-CARNITINE

(57) Abstract

The present invention describes a process for the industrial production of L-carnitine, comprising the enantioselective reduction of an alkyl 4-chloro-3-oxobutyrate or 4-chloro-3-oxobutyramide. The optically active 3-hydroxy derivative thus obtained is reacted with trimethylamine, obtaining crude L-carnitine, which is then finally purified. The catalyst used for the reduction is a complex of ruthenium bound to a penta-atomic bis-heteroaromatic system. The reduction reaction, performed in controlled conditions of hydrogen pressure, substrate concentration, temperature, and substrate: catalyst molar ratio, enables 4-chloro-3-hydroxybutyrate or 4-chloro-hydroxybutyramide to be obtained in a high yield. The process described, which leads to L-carnitine being obtained, is easily applicable on an industrial scale.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

Industrial process for the production of L-carnitine

FIELD OF THE INVENTION

The invention described herein relates to the synthesis of L-carnitine.

The subject of the invention is a process for obtaining this product, which can be easily implemented on an industrial scale.

STATE OF THE ART

Carnitine contains an asymmetry centre and can therefore exist in the form of two enantiomers, designated R-(-)-carnitine and S-(+)-carnitine, respectively. Of these, only R-(-)-carnitine is present in living organisms where it acts as a carrier for the transport of fatty acids across the mitochondrial membranes.

It is therefore essential that only R-(-)-carnitine be administered to patients undergoing regular haemodialysis treatment or treated for cardiac or lipid metabolism disorders.

In view of the substantial biological and pharmaceutical interest in this molecule, many studies have been conducted with a view to its synthesis.

The known techniques of large-scale synthesis of L-carnitine include:

i) the optical resolution of a racemic mixture: this technique involves the use of a resolving agent in an equimolar amount and the separation of the unwanted enantiomer. This procedure leads to the loss of 50% of the starting product.

ii) Stereospecific hydration of crotonobetaine or γ-

butyrobetaine by a microbiological method (US 4708936). This microbiological synthesis procedure entails the risk of imperfect reproducibility, of possible alterations of the strain used, and of possible biological contamination of the product.

iii) Enantioselective reduction of a butyric 4-chloro-3-oxoester by means of mono- or bimetallic ruthenium catalysts. This yields the corresponding 3-hydroxy derivative which, by reaction with trimethylamine and hydrolysis of the ester group, is converted to L-carnitine.

The reduction reaction mentioned in iii) has been the subject of several studies.

For example, patent EP-B-295109 describes the reduction of a 4-chloro-3-oxobutyrate with a catalyst containing ruthenium bound to a chiral diphosphine which in turn is bound to a bisnaphthalenic system; the valence of the metal is completed by a combination of halogens and triethylamine. The reaction is carried out at 30°C with a hydrogen pressure ranging from 40 to 100 kg/cm^2, with substrate:catalyst molar ratio of 1000:1, in a reaction time of 16-20 hours. The optical yield below 67% and the lengthy reaction times and high pressures involved make the process industrially unacceptable.

In patent application EP-A-339764, L-carnitine is obtained by means of a process comprising the reaction of a 4-halo-3-oxobutyrate with the above-mentioned ruthenium-based catalyst: the reaction is carried out at approximately 100°C, at a mean

pressure of 70-100 kg/cm^2, with a substrate:catalyst molar ratio ranging from 1000 to 10,000:1. The process described once again presents the disadvantage of having to operate at high pressure values. In addition, the overall carnitine yield with this method was modest (46%). Similar results are reported in Tetrahedron Letters, 29, 1555, (1988).

The synthesis methods described above not only present modest yields and, in the first case, also lengthy reaction times, but also involve operating at high hydrogen pressures, which increases the cost of the process and the safety precautions to be adopted. This problem becomes crucial when moving over from laboratory- to industrial-scale production.

A number of studies describe the reduction of β-ketoesters by means of ruthenium complexes catalysts, operating at moderate pressure values; the results. however, are unsatisfactory in terms of yields and/or reaction times, and these processes therefore cannot be applied on an industrial scale. In Tetrahedron Letters, 32, 4163, (1991), the reduction of 4-chloro-3-oxobutyrate with 4-atm. hydrogen pressure is described. The reduced product has an enantiomeric purity inferior to that obtained when operating at high pressure, and the reaction times are rather lengthy (6 h). The lower enantiomeric purity leads to a greater loss of L-carnitine yield. In EP-A-573184, the reduction of a terbutylic ester of the same substrate is carried out at a pressure of 10-15 kg/cm^2: the reaction is completed in two hours with an unsatisfactory yield and

enantiomeric purity.

Analysis of the above-mentioned technique reveals the lack of a process for the synthesis of L-carnitine which is easily and efficiently reproducible on an industrial scale. In particular, what is lacking is an L-carnitine synthesis process comprising the enantioselective catalytic reduction of 4-halo-3-oxobutyric derivatives of such a nature as to be carried out on an industrial scale with high yields and high enantiomeric purity and operating in moderate pressure conditions.

ABSTRACT OF THE INVENTION

The present invention discloses a process for the industrial production of L-carnitine, comprising the enantioselective reduction of an alkyl 4-chloro-3-oxobutyrate or 4-chloro-3-oxobutyramide. The optically active 3-hydroxy derivative thus obtained is reacted with trimethylamine, obtaining crude L-carnitine, which is then finally purified. The catalyst used for the reduction is a complex of ruthenium bound to a penta-atomic bis-heteroaromatic system. The reduction reaction, performed in controlled conditions of hydrogen pressure, substrate concentration, temperature, and substrate:catalyst molar ratio, enables 4-chloro-3-hydroxybutyrate or 4-chloro-hydroxybutyramide to be obtained in a high yield. The process described, which leads to L-carnitine being obtained, is easily applicable on an industrial scale.

DETAILED DESCRIPTION OF THE INVENTION

The subject of the invention described herein is a process for

the synthesis of L-carnitine. The first step in achieving the object of the invention consists in the enantioselective catalytic reduction of an alkyl 4-chloro-3-oxobutyrate or 4-chloro-3-oxobutyramide, according to the following diagram:

(I) (II)

where:

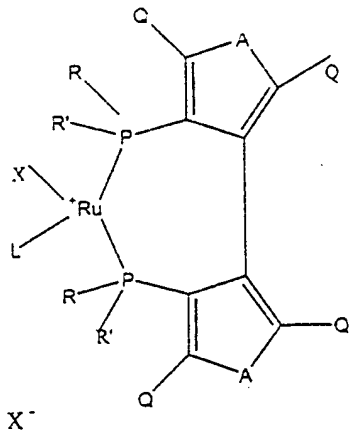
Y = OR_1, NH-R_1, N(R_1R_2)

R_1,R_2, equal or different = alkyl C_1-C_{10} alkylaryl and

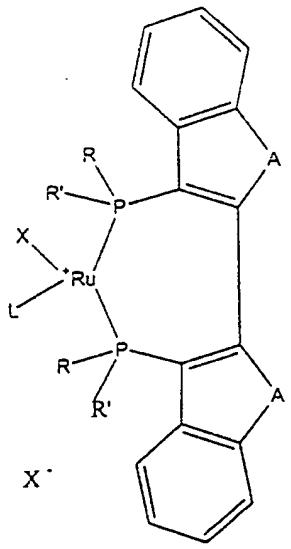
reaction of formula (II) derivatives with trimethylamine, with formation of L-carnitine.

The preferred starting substrate is ethyl 4-chloro-3-oxobutyrate (ethyl γ-chloro-acetoacetate).

The reduction reaction catalyst consists of a ruthenium complex bound to a penta-atomic bis-heteroaromatic system. This structure corresponds to one of the two formulas (III) or (IV).



(III)



(IV)

where:

A = S, O, NR_3, N-aryl, N-CO-R_3

R_3 = alkyl C_1-C_{10}, alkylaryl, aryl

Q = alkyl C_1-C_4, phenyl

R, R', equal or different = optionally alkyl-substituted phenyl, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or R and R' together form a 4-6 atom phosphorocyclic system

X and L, equal or different, have the following meanings:

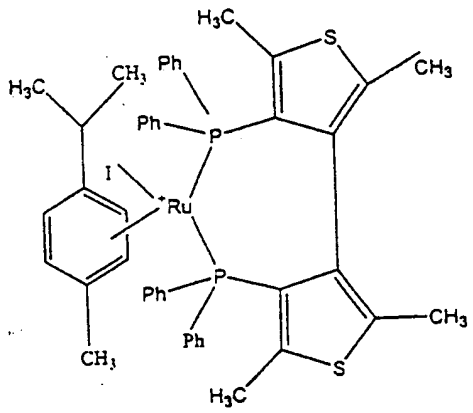
X = halogen, alkylsulphonate, arylsulphonate

L = halogen, aryl, π aryl, olefin system, η^3 allyl system, such as, for example, the 2-methylallyl system, carboxylate group, such as, for example, acetate or trifluoroacetate.

What is meant by the π aryl group is a type of direct co-ordination with the aromatic electron system, without any direct bonding of a carbon atom of the ring with the metal.

The formula (III) and (IV) compounds are described in patent application WO 96/01831, incorporated herein for reference.

In particular, the preference is for the use of catalysts where A represents S (3,3'-bisthiophenic structure), X represents halogen, particularly iodine, and L is an aryl system. The preferred catalyst is {[Ru (p-cymene) I (+) TMBTP] I}, represented by formula (V).



(V)

The reduction of alkyl 4-chloro-3-oxobutyrate or 4-chloro-3-oxobutyramide is done at a hydrogen pressure ranging from 2 to 7 bar, at a temperature ranging from 90 to 150°C, and with a substrate:catalyst molar ratio ranging from 5,000:1 to 30,000:1.

According to a preferred realisation of the invention, the reduction is performed at a hydrogen pressure of 5 bar, at a temperature of 120°C, and with a substrate:catalyst molar ratio between 10,000:1 and 15,000:1

The concentration of the substrate in the reaction mixture also

contributes towards obtaining the reduced product in a high yield and with high-grade optical purity. This concentration ranges from 5 to 15 g of substrate per 100 ml of solvent, and the preferred concentration is 10 g/100 ml.

The reaction mixture may advantageously contain catalytic amounts of a base.

The moderate hydrogen pressure conditions (on average 5 bar) make it possible to operate with simpler reactors and with less stringent safety conditions compared to similar reactions described in the known technique requiring a pressure of 100 atmospheres.

The process described herein proves easily reproducible on an industrial scale and does not require the use of any additional expedients, such as, for example, the use of acid co-catalysts.

The process according to the invention yields optically active alkyl 4-chloro-3-hydroxybutyrate or 4-chloro-3-hydroxybutyramide with a yield ≥ 95% and with e.e. ranging from 95 to 97%. As a result of the transformations described here below, these results make it possible to obtain the L-carnitine end product with an overall yield of 65-70%.

Furthermore, high substrate:catalyst ratios make it possible to operate with low amounts of catalyst, thus contributing to cost savings in the reaction process.

The alkyl 4-chloro-3hydroxybutyrate or 4-chloro-3-hydroxybutyramide obtained by catalytic reaction are subsequently converted to L-carnitine reaction of formula (II) derivatives by

reaction with trimethylamine.

The reduced derivatives are reacted with trimethylamine with formation of L-carnitine alkyl ester or alkyl amide. This reaction is performed preferably at temperatures from 55 to 90°C for time periods ranging from 1 to 70 hours. Particularly satisfactory results are obtainable when operating at 65°C for 60 hours, or at 80°C for 24 hours. According to the type of reactor used, stirring and loading conditions, reaction times of even 1-2 have been observed at 80°C.

The reaction entails the substitution of the 4-chloro with the 4-trimethylamine group for and hydroylsis of the ester or amide group, with the formation of crude L-carnitine, which is then purified to make it suitable for pharmaceutical use.

The purification can be done with known methods such as, for example, chromatography, extraction with solvents, ultrafiltration, and other equivalent methods.

Thanks to the advantages identified above, such as low pressure, high yields and high-grade optical purity, and the use of limited amounts of catalyst, the invention described herein makes it possible to produce L-carnitine efficiently and economically in large-scale industrial plant.

The invention is further described by means of the following examples.

EXPERIMENTAL PART

Example 1: Preparation of {[Ru (p-cymene) I (+) TMBTP] I}

a) Preparation of [Ru I_2 p-cymene]$_2$

Two g of [Ru Cl_2 p-cymene]$_2$ and 50 ml of methylene chloride are placed under nitrogen in a flask; 66 mg of tetramethylammonium iodide and subsequently an aqueous solution (50 ml) containing 10.2 mg of KI are added to the solution.

The mixture is left under vigorous stirring and in an inert atmosphere for approximately 15 hours at ambient temperature. The phases are separated. The aqueous phase is extracted with 2 x 40 ml of CH_2Cl_2. The gathered organic phases are washed with 3 x 40 ml of H_2O, dried on Na_2SO_4 and filtered on dicalite. A red-brown solution is obtained which is vacuum-dried. 3.07 g of [Ru I_2 p-cymene]$_2$ are obtained.

b) Preparation of {[Ru (p-cymene) I (+) TMBTP] I}

155 mg of [Ru I_2 p-cymene]$_2$ and 204 mg of (+) TMBTP are placed under nitrogen in a flask, and the mixture of 80 ml of CH_2Cl_2 and 30 ml of MeOH degassed with nitrogen is added. The mixture is left at reflux under stirring for 1.5 h; it is then cooled and concentrated at reduced pressure. The dark red solid consisting of {[Ru (p-cymene) I (+) TMBTP] I} is used as such in the enantioselective hydrogenation processes.

Example 2: Preparation of ethyl (+) (R)-4-chloro-hydroxybutyrate

100 g of ethyl 4-chloro-3-oxobutyrate and 64.9 mg of {[Ru (p-cymene) I (+) TMBTP] I}, prepared in example 1, are placed under argon in a 3-litre reactor, in 1000 ml of ethyl alcohol degassed with argon; the mixture is heated at 120°C under argon and pressurised with hydrogen at 5 bar. After 3 h, the mixture is cooled,

concentrated at reduced pressure, and the residue distilled with 5 mm Hg vacuum. 91 g of ethyl (+) (R)-4-chloro-3-hydroxybutyrate are obtained with an e.e. of 97% by gas-chromatography analysis.

Example 3: Preparation of L-carnitine

8.4 g (0.05 mol) of ethyl (+) (R)-4-chloro-3-hydroxybutyrate and 23 ml (0.18 mol) of 45% trimethylamine in H_2O are placed in a 50 ml-vial. The vial is closed with a rubber plug, sealed with a ring cap and maintained at 80°C for 24 h. At the end of the reaction the vial is cooled and opened. The aqueous solution is transferred to a flask, 20 ml of methylene chloride are added and the resulting solution is left overnight under stirring. The aqueous phase is then recovered and eluted on a chromatography column containing 200 ml of Amberlite IRA 402 resin activated in the form of HCO_3^-.

After elution of the first 30 ml, carnitine is eluted. The fractions containing L-carnitine (control TLC $CHCl_3$ 42, IsoprOH 7, MetOH 28, H_2O 10.5, AcOH 10.5), approximately 100-150 ml, are united and vacuum-concentrated. Isobutyl alcohol is used to form the azeotrope with water and completely eliminate the water.

The hygroscopic solid thus obtained is triturated with acetone and kept overnight under stirring with acetone. Filtration is performed and L-carnitine obtained with a final yield of 70%.

Examples 4-7

The hydrogenation procedure described in example 2 was repeated, changing the S:C ratios (Table 1), or operating with catalytic amounts of base (Table 2).

The results obtained are as follows:

TABLE 1

Hydrogenation reaction on 10 g catalyst:{[Ru(p-cymene) I (+) TMBTP] I} scale

Test	T	P	S:C	% conv/t	Conc.	e.e.	yield
4	120°C	5 bar	5000:1	100%/30 min	10%	96%	97%
5	120°C	5 bar	10000:1	100%/30 min	10%	96%	98%

Legends:

S:C : substrate:catalyst molar ratio

% conv/t : percentage substrate reduced/time

conc. : substrate concentration in reaction mixture

e.e. : optical purity of reduced product

The results in Table 1 show that, when operating with the catalysts described in the present invention, and under the reaction conditions indicated, it is possible to obtain ethyl 4-chloro-3-hydroxybutyrate in high yields and with high-grade enantiomeric optical purity.

TABLE 2

Hydrogenation reaction on 100 g catalyst:{[Ru(p-cymene) I (+) TMBTP] I} scale

Test	Base	T	P	S:C	% conv/t	Conc.	e.e.	Yied
6	No	120°C	5 bar	10000:1	100%/240 min	10%	96%	95%
7	Yes	120°C	5 bar	10000:1	100%/70 min	10%	95%	92%

Example 8: Preparation of ethyl (+) (R)-4-chloro-hydroxybutyrate

14 Kg of ethyl 4-chloro-3-oxobutyrate (titre 88%) and 6.2 g of {[Ru (p-cymene) I (+) TMBTP] I}, are placed under argon in a 200-litre reactor, in 143 l of ethyl alcohol. The mixture is heated at 116°C and pressurised with hydrogen at 5-6 bar. Temperature rises up to 124°C and the raction goes to completion within about 1 hour. The mixture is cooled, concentrated at reduced pressure, and the residue, analyzed with gaschromatography has a 81% titre of ethyl (+) (R)-4-chloro-3-hydroxybutyrate, with an e.e. of 96.7%. reaction yield: 94%.

Example 9: Preparation of L-carnitine

400 g of crude ethyl (+) (R)-4-chloro-3-hydroxybutyrate, prepared according to Example 8, and 1 l of 45% trimethylamine in H_2O are placed in a 2-litre reactor. The reaction mixture is heated to 80°C and kept at this temperature for 15 h. After cooling and removing the excess of trimethylamine under nitrogen flow, the aqueous solution is extracted with 1.9 l of methylene chloride and

analyzed with HPLC. L-carnitine is obtained with 75% yield.

Example 10: Preparation of L-carnitine

110 g of ethyl (+) (R)-4-chloro-3-hydroxybutyrate, prepared according to Example 2, and 280 ml of 45% trimethylamine in H_2O are placed in a 0.6-litre reactor. The reaction mixture is heated to 80°C and kept at this temperature for 2 h. After cooling and removing the excess of trimethylamine, the aqueous solution is extracted with 0.5 l of methylene chloride and analyzed with HPLC. L-carnitine is obtained with 71% yield.

CLAIMS

1. Process for the synthesis of L-carnitine comprising the following steps:

(a) enantioselective reduction of an alkyl 4-chloro-3-oxobutyrate or 4-chloro-3-oxobutyramide according to the following diagram:

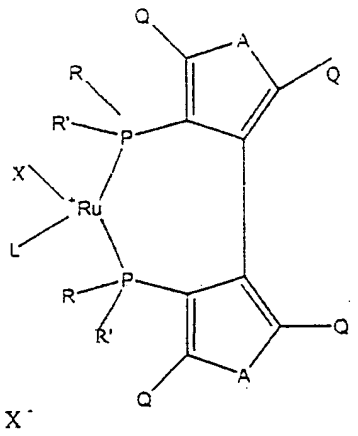
(I) (II)

where:

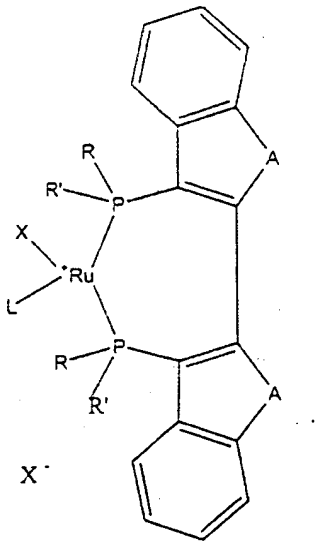
Y = OR_1, NH-R_1, N(R_1R_2)

R_1,R_2, equal or different = alkyl C_1-C_{10} alkylaryl

and where the reduction reaction catalyst consists of a ruthenium complex corresponding to one of the two formulas (III) or (IV)



(III)



(IV)

where:

A = S, O, NR_3, N-aryl, N-CO-R_3

R_3 = alkyl C_1-C_{10}, alkylaryl, aryl

Q = alkyl C_1-C_4, phenyl

R, R', equal or different = optionally alkyl-substituted phenyl, alkyl C_1-C_6, cycloalkyl C_3-C_8, or R and R' together form a 4-6 atom phosphorocyclic system

X and L, equal or different, have the following meanings:

X = halogen, alkylsulphonate, arylsulphonate

L = halogen, aryl, π aryl, olefin system, carboxylate

(b) reaction of formula (II) derivatives obtained in (a) with trimethylamine, with formation of L-carnitine.

2. Process according to claim 1, where reduction (a) is performed at a hydrogen pressure ranging from 2 to 7 bar;

temperature ranging from 90 to 150°C; substrate:catalyst molar ratio ranging from 5,000:1 to 30,000:1; substrate concentration in the reaction mixture ranging from 5 g/100 ml to 15 g/100 ml.

3. Process according to claim 1, where reduction (a) is performed at a hydrogen pressure of 5 bar; temperature 120°C; substrate:catalyst molar ratio 10,000:1-20,000:1; substrate concentration in the reaction mixture 10 g/100 ml.

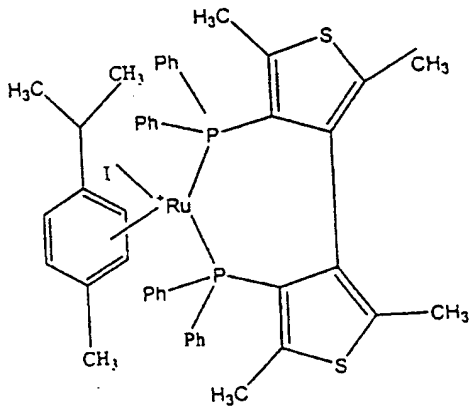
4. Process according to claim 1, where the reaction mixture in step (a) contains catalytic amounts of a base.

5. Process according to claim 1, where reaction (b) is carried out at a temperature of 65°C for 60 hours.

6. Process according to claim 1, where reaction (b) is carried out at a temperature of 80°C for 1-24 hours.

7. Process according to claim 1, where the L-carnitine obtained in (b) is further subjected to purification.

8. Process according to claim 1, where the catalyst is {[Ru (p-cymene) I (+) TMBTP] I}, represented by the following formula:



(V)

INTERNATIONAL SEARCH REPORT

Interi .nal Application No
PCT/IT 99/00365

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C227/32 C07C67/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 01831 A (ITALFARMACO SUD SPA ;ANTOGNAZZA PATRIZIA (IT); BENINCORI TIZIANA ( ) 25 January 1996 (1996-01-25) cited in the application page 16; claims 1,12-15; example 16 ---	1,8
A	EP 0 295 109 A (TAKASAGO PERFUMERY CO LTD) 14 December 1988 (1988-12-14) cited in the application claim 1; tables 1,2 ---	1-4,6,7
A	EP 0 339 764 A (TAKASAGO PERFUMERY CO LTD) 2 November 1989 (1989-11-02) cited in the application claim 1; table 1 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2000	22/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rufet, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ional Application No
PCT/IT 99/00365

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 375 417 A (TAKASAGO PERFUMERY CO LTD) 27 June 1990 (1990-06-27) page 7 -page 8	1-3,5-7
A	US 5 614 641 A (GENET JEAN-PIERRE ET AL) 25 March 1997 (1997-03-25) claim 1; examples 2-4; table 1	1
A,P	WO 99 52915 A (GANCIA EMANUELA ;CHEMI SPA (IT); PICCOLO ORESTE (IT); ZALIANI ANDR) 21 October 1999 (1999-10-21) page 1 -page 2; claims 1-11,22; figures 1-3	1,8
A	M. KITAMURA ET AL.: "Convenient preparation of BINAP-Ruthenium (II) complexes catalyzing asymmetric hydrogenation of functionalized ketones" TETRAHEDRON LETTERS., vol. 32, no. 33, 1991, pages 4163-4166, XP002132496 OXFORD GB cited in the application page 4165; table 1	1-3

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ...nal Application No
PCT/IT 99/00365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601831 A	25-01-1996	IT 1270082 B	28-04-1997
		AT 184878 T	15-10-1999
		AU 685660 B	22-01-1998
		AU 3076495 A	09-02-1996
		CA 2193889 A	25-01-1996
		CN 1190397 A	12-08-1998
		CZ 9700083 A	11-06-1997
		DE 69512415 D	28-10-1999
		DE 69512415 T	05-01-2000
		EP 0770085 A	02-05-1997
		HU 75997 A	30-06-1997
		JP 10502387 T	03-03-1998
		US 5907045 A	25-05-1999
EP 0295109 A	14-12-1988	JP 1964647 C	25-08-1995
		JP 6099367 B	07-12-1994
		JP 63310847 A	19-12-1988
		DE 3868700 A	09-04-1992
		US 4933482 A	12-06-1990
EP 0339764 A	02-11-1989	JP 1211551 A	24-08-1989
		JP 1944040 C	23-06-1995
		JP 6078277 B	05-10-1994
		US 4895979 A	23-01-1990
EP 0375417 A	27-06-1990	JP 1910357 C	09-03-1995
		JP 2169555 A	29-06-1990
		JP 6041445 B	01-06-1994
		DE 68908129 T	03-03-1994
US 5614641 A	25-03-1997	FR 2693190 A	07-01-1994
		AT 148091 T	15-02-1997
		CA 2139361 A	20-01-1994
		DE 69307706 D	06-03-1997
		DE 69307706 T	24-07-1997
		EP 0648201 A	19-04-1995
		ES 2099453 T	16-05-1997
		WO 9401390 A	20-01-1994
WO 9952915 A	21-10-1999	IT MI980773 A	11-10-1999
		AU 3814799 A	01-11-1999